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Disease Burden of Relapsing-Remitting Multiple Sclerosis

EPIDEMIOLOGY

Multiple sclerosis (MS) is a central nervous system (CNS) disorder that involves inflammation, demyelination, and degenerative changes that eventually lead to disability if untreated.¹ Approximately 300,000 to 400,000 individuals are thought to be affected by MS in the United States, but a 2017 estimate of prevalence based on observed increases in Department of Veterans Affairs and Intercontinental Marketing Services data sets, suggests that up to 913,925 individuals could be affected by MS in the United States.²

MS is often diagnosed in individuals between 20 and 40 years of age, with women accounting for approximately two-thirds of cases; however, onset can also occur in pediatric and older adult age groups.^{1,3} Although a higher rate of MS has been observed in White Americans than other racial groups (eg, Asian Americans and Hispanic Americans),⁴ recent studies suggest that Black women have a higher risk than previously reported and Black and Hispanic patients may have more rapid disease progression than White patients.^{1,4}

DISEASE COURSE AND IMPORTANCE OF EARLY TREATMENT

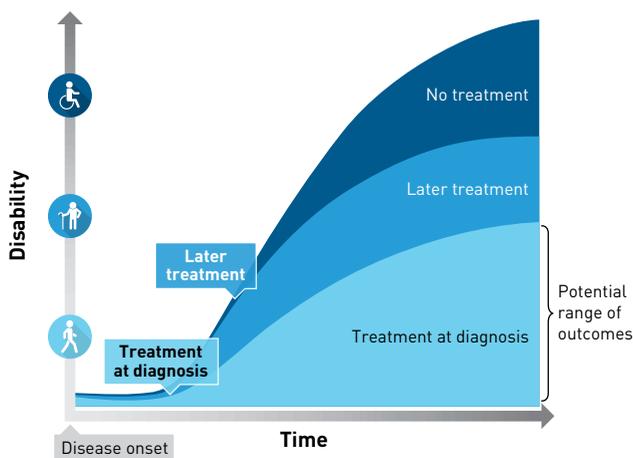
Although the course of MS varies, 85% to 90% of patients present with a pattern of relapses and remissions of neurologic symptoms in the early stages of the disease, with clinical events that are usually associated with CNS inflammation.¹ If untreated, this relapsing-remitting course is followed by a pattern of progressive worsening with few relapses or magnetic resonance imaging (MRI) activity, which is known as secondary progressive MS.¹ Prompt treatment to minimize disease relapses in the early stages is essential because the mechanisms of CNS repair and remodeling that can partially compensate for the MS-induced damage in the early stages do eventually fail to keep up, leading to steady progression of physical and mental disability without remission (Figure 1).³ Relapses in the first few years of the disease have been associated with the future level of disability, and a short interval of time between the first and second relapse is a strong predictor of disability progression.³ In the relapsing-remitting course, MS is often characterized by actively demyelinating plaques associated with inflammation and disruption to the blood-brain barrier. These plaques (or lesions) tend to shrink over time in chronic MS, and this loss of lesion volume is a key contributor to brain atrophy.⁵

BURDEN OF DISABILITY

In relapsing-remitting MS, symptoms that appear in the form of relapse (also known as an attack or bout) may include sensory symptoms (eg, numbness, tingling, or burning pain), motor symptoms (eg, weakness, stiffness, clumsiness, difficulty walking, impairments in speech and swallowing), visual disturbances, physical or mental fatigue that interferes with daily activities, mood disorders (eg, depression and anxiety), genitourinary and bowel dysfunction, tremor, and stiffness, among others (Figure 2).³

Symptoms associated with relapses often develop over a period of a few days, followed by a plateau; they subside over the next several weeks or months.³ During this time, neurological

Figure 1. Trajectory of Disability Outcomes With Early, Late, and No Treatment³



reserve and repair mechanisms enable remodeling and compensate for damage to the CNS. Although complete recovery often occurs in the early stages of MS, relapses may also result in sustained increases in disability, and incomplete recovery (due to exhaustion of neurological reserve) contributes to stepwise progression in disability. If relapsing-remitting disease transitions into secondary progressive MS, disability (particularly the ability to walk) worsens progressively independent of relapse activity.³ Without treatment, 50% to 60% of patients with relapsing-remitting MS develop secondary progressive disease within 15 to 20 years and, on average, lose the ability to walk unassisted for 100 meters after 14 years.³

Disability in patients with MS is typically assessed using the Expanded Disability Status Scale (EDSS), which assigns higher numeric values to greater levels of physical disability when assessing functional capacity in the pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other systems.⁶ However, MS may negatively affect several other quality-of-life measures that are not adequately measured by EDSS, including cognition, vitality, mental health, and fatigue. Cognitive impairment in early-stage MS may reduce quality of life, negatively affect activities of daily life, and reduce the ability to work.³ Approximately 75% of patients with MS experience persistent or sporadic fatigue that often leads to lower quality of life.³

Rates of unemployment are also higher in patients with MS than in the general population, even among those with low levels of physical disability, suggesting that the cognitive impairment, fatigue, depression, and anxiety related to MS may negatively affect gainful employment.³ Furthermore, MS is associated with substantial indirect economic costs that may include loss of earnings by the patient's unpaid caregiver, early withdrawal from an active lifestyle, and loss of productivity.⁷

UTILITY OF BIOMARKERS

Biomarkers for prognosis of MS may provide information about disease activity and whether conversion to another form of MS has occurred.⁸ Although some biomarkers have been shown to correlate with diagnosis and monitoring of disease activity, none have been shown to be specific for MS or to reliably predict an individual patient's response to a therapy.^{8,9} For example, presence of oligoclonal bands in cerebrospinal fluid is predictive of conversion from clinically isolated syndrome (CIS) to MS and can be used to rule out other diagnoses and prognosticate conversion from CIS.⁹ White matter lesions on MRI indicate progression from CIS to clinically defined MS, although the relationship between T2-weighted white matter lesion load and clinical disability measured by EDSS varies among studies.⁹ There are some biomarkers of neurodegeneration that have been shown to correlate with disease severity and progression, but they do not predict relapses (which limits their clinical utility), because they generally fluctuate in correlation with disease activity that trails behind clinical relapses.⁹

MANAGEMENT OF MS

Comprehensive management of MS includes nonpharmacologic and pharmacologic therapies. Proper care contributes to the overall health of patients with MS and can impact disease progression and lifespan.³

Nonpharmacologic

To ensure the best outcomes in MS, it is important for patients to maintain a healthy diet, exercise, stop smoking, and lose weight (if indicated).^{3,10} Preventive care (such as immunizations) and the management of other medical conditions are also key.¹⁰ Patients with MS should also have access to programs that support their physical and emotional well-being.¹¹ These include rehabilitation programs that promote functional mobility, safety, and independence for patients with MS (eg, speech and swallowing, memory and other cognitive functions). Mental health providers can lend support and education; they can also diagnose and treat depression, anxiety, and other conditions that are frequent in patients with MS.

Pharmacologic

Pharmacologic therapies for MS fall into 3 categories: those that treat relapses, those that target specific symptoms, and, most importantly, those that can modify the disease course (ie, disease-modifying therapies [DMTs]).¹² Although mild relapses may not substantially impact daily activities or require treatment, severe attacks often necessitate a short course of intravenous or oral corticosteroids.¹³ Patients with MS can experience a multitude of symptoms and may require medications to manage them.³

DMTs

Although no cure is available for MS, DMTs can reduce disease activity and slow the rate of progressive disability.³ Long-term studies show that early intervention with DMTs increases the likelihood of a

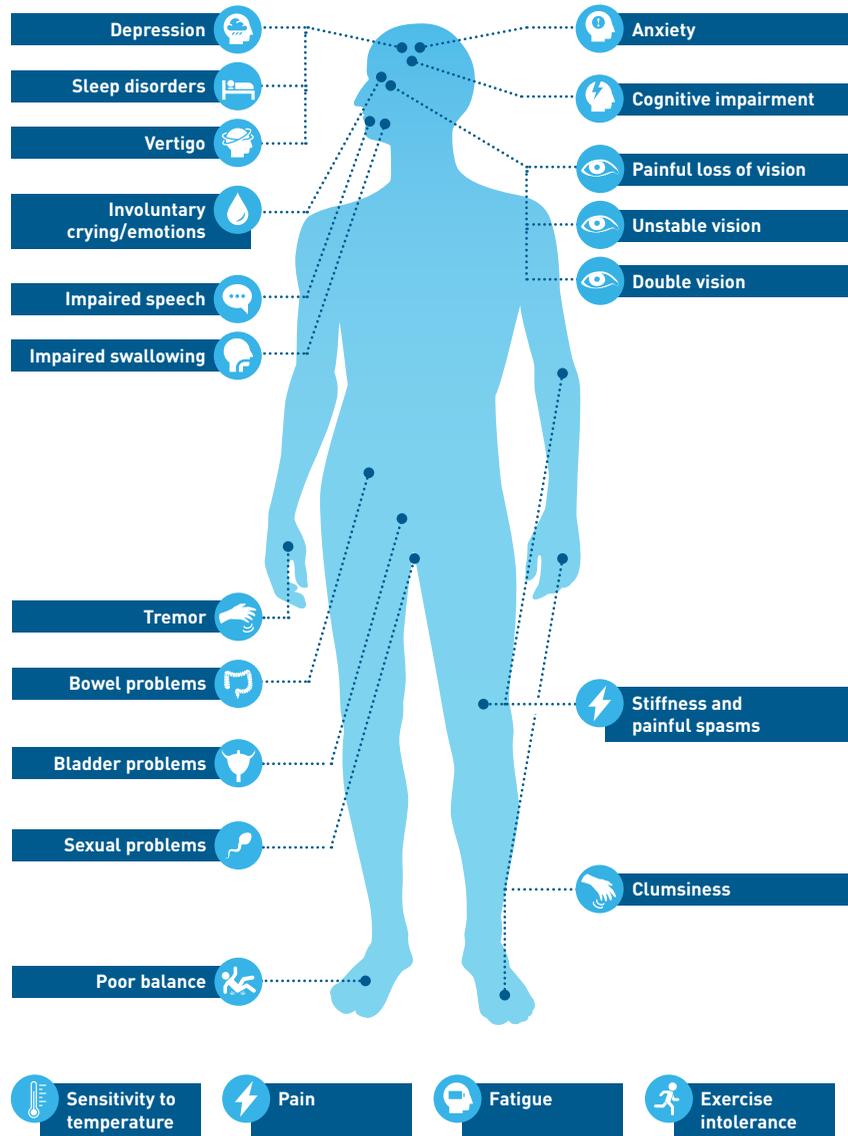
favorable outcome compared with delayed intervention in patients with CIS or relapsing-remitting MS.³ DMTs have also been shown to increase time to second relapse and improve MRI outcomes, such as brain atrophy rate, in patients with CIS.³ Furthermore, DMTs have been shown to be more effective for slowing progression of disability in younger versus older patients and reducing the rate of relapse in younger (vs older) patients, patients with low (vs high) EDSS scores, and those with active lesions (vs no active lesions).³

GUIDELINE RECOMMENDATIONS FOR DMTs

Early, aggressive, and ongoing treatment with DMTs is important to reduce clinical and subclinical attacks and delay the onset of the progressive phase of disease, thereby helping to prevent onset of disability, prolong activity and engagement, and maintain quality of life.¹ A 2018 report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology (AAN) recommended offering DMTs to patients with relapsing forms of MS who have had recent relapses and/or MRI activity, including those with 1 clinical episode who fulfill the 2010 International Criteria for MS, because of the demonstrated benefits with reducing relapses and MRI activity.¹⁴ Additionally, DMTs are associated with a delay in a second clinical relapse or new MRI-detected brain lesions in patients with a single demyelinating event and 2 or more MRI-detected brain or spinal cord lesions.¹⁴

Key goals of DMT for MS include reducing subclinical disease activity, minimizing loss of brain volume, and slowing disability progression. Early diagnosis enables initiation of DMT along with lifestyle interventions to preserve brain tissue and health and management of comorbidities such as blood pressure.³ According to AAN guidelines, choosing a DMT should involve shared decision-making between the patient and clinician, because considering patient preferences may help improve acceptance of and adherence to DMTs.¹⁴ Additionally, the AAN guidelines recommend that clinicians inform patients of the appropriate expectations of DMTs (ie, that they do not completely eliminate disease relapse and MRI activity) and possible need for additional treatment to address disease-related symptoms. After starting a DMT, clinicians should continue to monitor patients regularly for adherence, potential barriers

Figure 2. Common Symptoms Associated With Multiple Sclerosis³



to adherence, adverse events, tolerability, safety, and effectiveness.¹⁴ Reproductive plans should also be discussed and considered when selecting DMTs in patients of childbearing age.¹⁴

SUMMARY

MS typically progresses over time and can lead to irreversible disability if untreated; therefore, a comprehensive management plan that incorporates preventive care, healthy lifestyle choices, and prompt initiation of DMT is essential to slow progression of disease and

optimize quality of life, physical function, and cognition. Ongoing follow-up and communication between the patient and provider are important to minimize disease activity and clinical symptoms and maximize patient quality of life. •

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Expert Perspectives on Disease Burden of Relapsing-Remitting Multiple Sclerosis: A Q&A With Jonathan C. Calkwood, MD



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***The American Journal of Managed Care*[®]: What are some specific patient characteristics associated with relapsing-remitting multiple sclerosis (MS)?**

Jonathan C. Calkwood, MD: In general, female predominance of the disease, at least in the relapsing forms, and onset in early to mid-adulthood is the well-known demographic of MS. The prognosis for an individual with MS can be highly variable and can be hard to predict. The disease is characterized by intermittent neurological attacks and recoveries which progress to permanent physical and cognitive disability. The patient characteristics associated with relapsing-remitting MS that interest me most are those characteristics that help me understand where a patient is currently in their disease course as well as those that help me predict a patient's risk of disability. To me, the important characteristics are those that are predictive of long-term accumulation of disability. How do I predict where that patient might be? If I have someone with aggressive disease, I want to match that disease aggressiveness with an appropriately efficacious treatment. Now, that might beg the question, "If highly efficacious treatments preserve neurons and prevent more disability, when should we use a less efficacious treatment?" The question I often ask other neurologists who might be reluctant to make a treatment change is, "How many brain cells is it ok to lose on a lesser efficacious treatment that we might have prevented?" The answer should be zero and current research strongly supports early intervention with highly efficacious therapies to limit development of disability.

There are three patient characteristics that I am most concerned with: relapses, magnetic resonance imaging (MRI) lesions, and the level of disability based on neurological exams. I focus on those characteristics that are predictive of a more aggressive disease including: race, frequency of exacerbations, incomplete recovery from a relapse, or more severe relapses. The character of the patient's neurological symptoms, be it relapses or their day-to-day

symptoms, can help us. Patients who have symptoms or relapses with predominantly involved symptoms that are coming from their brainstem or their spinal cord may have more disabling issues. It's the same for MRI characteristics. If lesions are accumulating in the brainstem and the spinal cord, that patient is at higher risk for physical disability. We also use a patient's neurologic exam abnormalities in a similar way. There are many risk factors that may exist in an individual that may influence risk assessment so it is important to form a type of a "matrix" of what those characteristics are to try to identify a higher-risk patient.

***AJMC*[®]: What do you see as existing gaps in care for patients with relapsing-remitting MS?**

Jonathan C. Calkwood, MD: There are many gaps in our health-care system that may influence a patient's ultimate accumulation of disability. I think there is a huge gap that readers of *AJMC*[®] could, and should, influence. The healthcare insurance industry attempts to apply utilization management practices that work well in many other disease states but are fundamentally flawed when applied to MS. Individual patient variability in a disease state like diabetes or hypertension is relatively uniform compared to MS. These diseases have easily measured and inexpensive biomarkers that tightly correlate with outcome. In these diseases, you can identify a treatment failure before there is permanent end organ damage. Selectively limiting access to treatments is less likely to have permanent consequence for the patient with diabetes or hypertension when end organ damage can be predicted by biomarkers. Treatment escalation based on efficacy, cost, or treatment risk has little if any long-term consequences for the patient and makes sense in these diseases where treating to those biomarkers prevents end organ damage in the future.

In MS, the measure of treatment failure is end organ damage. We grow all the brain cells we have by the age of 19 to 21 years of age. Neurons, unlike other tissues in our body, do not have the capacity to regenerate. In MS, a new lesion on the MRI, a relapse, worsening on neurological exam, cognitive decline, or other changes indicate that the patient has already lost brain cells.

Even as an expert in MS, it is difficult to predict how an individual patient is going to progress, but I can put them in a higher risk group. As such, we should treat patients proactively to prevent disability accumulation.

I believe the single biggest clinical gap in care is the limited access to classes of therapy or individual medications that may be medically determined by the physician as appropriate for an individual patient. Since more efficacious treatments have demonstrated better outcomes, we want to use the most efficacious treatment early in the course of disease that is appropriate for that individual patient.

Other important gaps in care are access to MRIs and medications because of the financial burden it puts on them. A patient with MS is usually on multiple symptomatic medications, so they're paying copays on those medications, too.

Another gap in care is the support of insurance companies of nonpharmacological measures, which have been proven to reduce disability. Some structure is needed that encourages patients with disabilities to participate in wellness programs (eg, physical therapy, exercise programs focused for patients with MS and disabilities, etc).

AJMC®: If left untreated, what is the course of disease for patients with relapsing-remitting MS?

Jonathan C. Calkwood, MD: If left untreated or undertreated, the data have been very clear that patients do worse and accumulate disability. Our earliest studies on disease-modifying therapies involved a placebo control group. With the very earliest studies on platform therapies, we saw the same thing when there was a placebo-controlled trial. Even if that study is only a year long, we will see on the Kaplan-Meier curve a separation between the 2 groups of patients in terms of their disability, MRI, or relapse rates that shows the difference between a patient who's on treatment versus not on treatment. Typically, in those studies, the patients in the placebo group rolled into a treatment trial or the treatment group for an extension study. When we put the patients taking placebo on treatment, they paralleled the other group, but at a significantly higher rate of disability. Even a delay in treatment of 1 or 2 years makes a difference in the disability progression of a patient with MS.

AJMC®: How quickly will symptoms develop in these patients if they're left untreated?

Jonathan C. Calkwood, MD: It's really unpredictable but virtually every patient will worsen more than they would have to if they weren't on a treatment or if incomplete efficacy is not addressed.

We have an older MS disability scale that attempts to predict progression—the MS severity scale. This is a “natural history scale” of the disease untreated. It is a tool to gauge the risk of progression by essentially gauging the length of time they had MS against their disability score. If we don't treat those people early, the data have been very clear that they will do worse and accumulate disability. The disability score is the Expanded Disability

Status Scale, which is used in most clinical trials and can be used to gauge the risk of the individual patient. I think the best indication would be if I'm able to gauge that individual's overall MS risk and disability based on the MS severity scale. It is important to monitor the patients to see how quickly disability is evolving while they are on treatment. These scales can be helpful but have significant limitations to predict an individual patient's future disability, and to help determine a treatment approach to match the aggressiveness of the disease.

MS can be more inflammatory in adolescents and young adults—their symptoms may change very quickly. I have a tendency to use more efficacious therapies in these patient types as I am more concerned about the risk of disease progression. Postpartum mothers are another high-risk group. Then there are those patients who aren't necessarily relapsing but they're neurologically worsening, seemingly relentlessly, despite our most efficacious treatments. The progressive patients with MS that are incompletely responsive to our current treatments represent a challenging group of patients to treat. We are sometimes left with supportive care measures alone.

While we commonly talk about physical symptoms, we also have to consider cognitive symptoms which develop from the onset of disease, but may not be visible until later in life. Early and effective treatment is necessary to preserve the brain cells and neurologic function. The brain of a patient with MS can atrophy at a faster rate than non-MS patients and have a greater risk for losing neurologic function sooner. If you have patients on a less efficacious therapy, their disease may not be controlled. Time equals brain cells, and we can't grow those neurons back. While it's hard to predict how quickly symptoms will develop when a patient is untreated, it doesn't matter if they're developing symptoms or not because they're losing brain cells faster. If they're not on the appropriate treatment, this results in more brain loss and greater levels of disability.

AJMC®: Could you provide a couple of examples of how relapsing-remitting MS affects patients' quality of life?

Jonathan C. Calkwood, MD: I think the two most underappreciated areas that affect quality of life of patients with MS are fatigue and cognitive dysfunction.

The most profound, universal impact is fatigue. A symptomatic issue with MS that we really don't understand very well but profoundly affects the ability of many patients to fully participate in work, life and relationships. Fatigue is commonly cited as a reason that a person with MS chooses to leave the work force.

The cognitive decline that I alluded to scares me the most because it's silent, and it really creeps up. We've got very crude tools for assessing cognitive functioning. We don't have a very good clinical metric, and by the time the person with MS has cognitive symptoms, they already lost many brain cells. We may

not have good biological markers. Brain atrophy is a trailing indicator of disease severity but is linked with fatigue and cognitive dysfunction. By the time we can measure brain atrophy, we're well behind the curve. That's one of the bigger, more worrisome quality-of-life issues, because cognitive dysfunction is pervasive in patients with MS, as early as clinically isolated syndrome.

A third aspect of MS on quality of life is physical disability. Some people with MS can be cognitively functioning but physically disabled or, on the flip side, they could look fine but be cognitively disabled. I have plenty of patients who have significant gait limitations, yet they're still fully functioning in the workforce. They're cognitively intact and are able to do highly cognitive jobs, yet physically they need to ride a scooter to get from the parking lot to their desks. MS manifests very differently in different people.

AJMC®: What utility do biomarkers have for patients with relapsing-remitting MS?

Jonathan C. Calkwood, MD: At this point in time, immune system biomarkers measured by laboratory tests are of limited usefulness in MS because we just don't understand the immune system abnormalities in MS well enough. That's where MRI, relapse rates, disabilities, and monitoring response to treatment come into place as biomarkers. I think one of the problems in MS is we're managing the patient with a reactive approach. From a neurologist's perspective, treating a patient with MS is like driving a bus while looking through the rearview mirror. We are always responding to what has already injured the patient's brain. We don't have good, predictive biomarkers so we're often responding after a patient has developed more disability. That's why we're often left using scales like the MS severity scale, the risk factor assessment, and a patient's individual risk factors. If someone had a relapse, the biomarker could be a change on MRI. That's probably our biggest, most useful biomarker because the brain MRI scans will show us lesions in the absence of new symptoms. The MRI is an effective biomarker, to help us define and identify an inadequate response to treatment, so we can then escalate therapy. But even an asymptomatic lesion can cause permanent loss of precious neurons.

The ideal biomarker would identify an inadequate response to therapy and warn us that a patient was headed for trouble before they lost brain cells. The biomarker of interest recently has been neurofilament light chains, which are proteins normally only found inside of nerve cells. These proteins are increased in the spinal fluid and blood of people with MS. The FDA has recently granted fast track review of a commercial lab test for neurofilament light. There is still a lot to learn, changes in neurofilament light chain correlates with disease activity and may be predictive for an individual or as a biomarker to distinguish relapses. Obviously, the neurofilament lights are going up in the blood or

“Some people with MS can be cognitively functioning but physically disabled or, on the flip side, they could look fine but be cognitively disabled. I have plenty of patients who have significant gait limitations, yet they're still fully functioning in the workforce. They're cognitively intact and are able to do highly cognitive jobs, yet physically they need to ride a scooter to get from the parking lot to their desks.”

in the spinal fluid because brain cells are dying; those neurofilament light chains belong inside nerve cells. We can at least use that as a general biomarker now, but it is yet another example of a biomarker indicating that the end organ has already been irreversibly damaged.

AJMC®: What nonpharmacologic approaches do you think are helpful in your patients?

Jonathan C. Calkwood, MD: It takes a village to care for a person with MS. They require so much support. The care provider and support partners of persons with MS deserve enormous credit. Education, social and psychological support provided by MS nonprofits and MS nurses are an important source of support. A neurologist trying to take care of people with MS can't just be a neurologist. We already talked about how you have to be an immunologist. Sadly, our patients, despite our best efforts, become disabled, and we have to understand physical medicine and rehabilitation. I would say probably one of the single biggest positives coming out of the neurologic literature in the past decade, but especially the last 5 years, has been a broadening of our approach to focus on biological and immunologic systems. Now we postulate, “What's the impact of general health and wellness on persons with MS?” As we have learned, the data on smoking have trickled out in MS. It's not just the other health issues associated with combustion products of tobacco. Smoking tobacco makes the immune system more aggressive.

Recently, we have identified obesity to be an immunologic issue for patients with MS. The immune system becomes more aggressive. Managing the patient's general medical issues, managing their quality of life, and managing exercise is absolutely one of the most important things. We've known about that

for quite a long time. People with MS will go into a slow downward spiral just from inactivity, so regular exercise is important.

Here's an example. When I joined Randall T. Schapiro, MD, FAAN at the Schapiro Center for MS, we had a program called the "Back to Fitness" program. That program took patients who had wrapped up physical therapy, but they still weren't back to where they were prior to their MS relapse, or, in some cases, they just became deconditioned. Here in Minnesota the winters are long and hard and people with MS may lose function quickly if they are not able to exercise and be active. Every spring, we get calls from our patients. They'd say, "I need steroids." I'd say, "Well, why do you need steroids?" "I can't walk to the mailbox anymore," they'd say. I'd ask, "Well, when was the last time you walked to the mailbox?" "Last September," they'd answer, and it was April. The patient hadn't been active, so we got them into physical therapy. That Back to Fitness program was hugely cost-effective. We had an exercise physiologist who would spend 3 days a week for a couple of weeks taking that patient into the gym and showing them how to exercise. Then patients could use a community health club to do their own therapy. The program reduced steroid use and side effects, reduced fall risk, gave patients a transition from physical therapy, and kept me from having to order physical therapy. It was cost-effective and benefitted patient overall well-being.

In addition to access for pharmacological therapies, a comprehensive approach to the disease should include support for health and wellness, access to primary care and internal medicine services for comanagement of medical conditions, smoking cessation, diet, and exercise. These interventions could help these patients more by helping them learn how to do those things that are going to maintain their health better, prevent disability, and lower cost to the healthcare system and society.

AJMC®: How do you decide on the appropriate pharmacologic treatment for your patients?

Jonathan C. Calkwood, MD: It starts from having an accurate diagnosis. Once we have made a diagnosis, I try and assess a patient's risk of future disability. If the risk is high, we definitely want to use a stronger treatment, even if the treatment comes with some risk. The majority of what I do, day in day out, is risk management for my patients. I can't really predict what's going to happen to them, and I can only put them in a higher or lower risk group based on the factors I mentioned earlier.

When I meet a patient with MS for the first time, the first thought process I go through is, "Do they have MS?" And then, "Are they on the right disease-modifying therapy?" By that, I mean the right efficacy. I think selecting the treatment for the patient starts from that—matching the treatment, the risk of the disease, and the risk of the treatment at some level.

The risk of treatment is not just adverse effects and lab abnormalities. The risk of a less efficacious treatment, may be disability for the patient with MS. If we can't truly predict how an individual is going to do, should we plan and treat for the best or worst potential outcome? If it is my brain we are talking about, I am going to want to err on the side of prophylaxis against the worst possible outcome. If I have a game plan that they have mild disease, and I'm wrong, they get more disabled. If I have a game plan for the worst-case scenario, and I'm not putting the patient at inordinate risk from the therapy and then it doesn't happen, is the patient any worse off? No, as long as you pay attention to risk, tolerability, adverse effects, and cost.

Based on research data and my experience, I prefer to use the higher-efficacy therapies early in the course of disease. It does not make sense to me to let a patient lose brain cells that we could otherwise prevent. The neurology community is in the process of making a 180-degree turn away from a treatment approach that starts with less efficacious therapies and escalates treatment as disease progresses to starting with higher-efficacy therapies. Among the MS specialists, we are making a change, but it's slow going. •

